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## NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

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ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing:

19 November 1998 (19.11.98)

International application No.:

PCT/EP98/02808

Applicant's or agent's file reference:

980724WO Me/gn

International filing date:

13 May 1998 (13.05.98)

Priority date:

14 May 1997 (14.05.97)

Applicant:

MÜLLER, H., W. et al

1. The designated Office is hereby notified of its election made:



in the demand filed with the International preliminary Examining Authority on:

30 September 1998 (30.09.98)



in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was

was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO  
34, chemin des Colombettes  
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer:

J. Zahra

Telephone No.: (41-22) 338.83.38

# PATENT COOPERATION TREATY

WO 98/31700  
PCT/EP98/02808

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From the INTERNATIONAL BUREAU

## NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

To:

MEYERS, Hans-Wilhelm  
P.O. Box 10 22 41  
D-50462 Köln  
ALLEMAGNE

30 NOV 1998

30 NOV 1998

1145.88

Date of mailing (day/month/year) 19 November 1998 (19.11.98)		
Applicant's or agent's file reference 980724WO Me/gn		IMPORTANT NOTICE
International application No. PCT/EP98/02808	International filing date (day/month/year) 13 May 1998 (13.05.98)	Priority date (day/month/year) 14 May 1997 (14.05.97)
Applicant MÜLLER, H., W. et al		

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:  
AU, BR, CA, CN, EP, IL, JP, KP, KR, NO, PL, US

In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:  
AL, AP, BA, BB, BG, CU, CZ, EA, EE, GE, GW, HU, ID, IS, LC, LK, LR, LT, LV, MG, MK, MN, MX, NZ, OA, RO, SG, SI, SK, SL, TR, TT, UA, UZ, VN, YU

The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on  
19 November 1998 (19.11.98) under No. WO 98/51708

### REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, a demand for international preliminary examination must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

### REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the national phase, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer J. Zahra
Facsimile No. (41-22) 740.14.35	Telephone No. (41-22) 338.83.38

## PATENT COOPERATION TREATY

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From the INTERNATIONAL BUREAU

NOTIFICATION CONCERNING  
SUBMISSION OR TRANSMITTAL  
OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

MEYERS, Hans-Wilhelm  
P.O.Box 10 22 41  
D-50462 Köln  
Germany  
ALLEMAGNE

Date of mailing (day/month/year) 22 July 1998 (22.07.98)	<b>IMPORTANT NOTIFICATION</b>
Applicant's or agent's file reference 980724WO Me/gn	
International application No. PCT/EP98/02808	
International publication date (day/month/year) Not yet published	
International filing date (day/month/year) 13 May 1998 (13.05.98)	Priority date (day/month/year) 14 May 1997 (14.05.97)
Applicant MÜLLER, H., W. et al	

1. The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).
2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.
3. An asterisk (\*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.
4. The letters "NR" appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

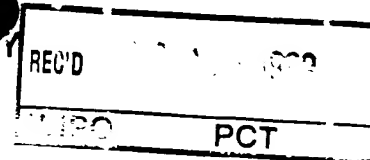
<u>Priority date</u>	<u>Priority application No.</u>	<u>Country or regional Office or PCT receiving Office</u>	<u>Date of receipt of priority document</u>
14 May 1997 (14.05.97)	971 07 846.4	EP	09 July 1998 (09.07.98)

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Marc Salzman
Facsimile No. (41-22) 740.14.35	Telephone No. (41-22) 338.83.38

Form PCT/IB/304 (July 1998)



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## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 980724wo Me/gn		<b>FOR FURTHER ACTION</b>	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA.416)
International application No. PCT/EP98/02808	International filing date (day/month/year) 13/05/1998	Priority date (day/month/year) 14/05/1997	
International Patent Classification (IPC) or national classification and IPC C07K16/18			
Applicant MÜLLER, H.W. et al.			
<p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 7 sheets, including this cover sheet.</p> <p><input checked="" type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of 4 sheets.</p>			
<p>3. This report contains indications relating to the following items:</p> <ul style="list-style-type: none"> <li>I <input checked="" type="checkbox"/> Basis of the report</li> <li>II <input type="checkbox"/> Priority</li> <li>III <input type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</li> <li>IV <input type="checkbox"/> Lack of unity of invention</li> <li>V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</li> <li>VI <input type="checkbox"/> Certain documents cited</li> <li>VII <input checked="" type="checkbox"/> Certain defects in the international application</li> <li>VIII <input checked="" type="checkbox"/> Certain observations on the international application</li> </ul>			
Date of submission of the demand  30/09/1998		Date of completion of this report  22.06.99	
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. (+49-89) 2399-0 Tx: 523656 epmu d Fax: (+49-89) 2399-4465		Authorized officer  Hoesel, H  Telephone No. (+49-89) 2399 8693 	

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/EP98/02808

**I. Basis of the report**

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

**Description, pages:**

1-14 as originally filed

**Claims, No.:**

1-17 as received on 26/05/1999 with letter of 25/05/1999

**Drawings, sheets:**

1/4-4/4 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:  
☐ the claims, Nos.:  
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/EP98/02808

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

**1. Statement**

Novelty (N)	Yes:	Claims	4 - 6, 13 - 17
	No:	Claims	1 - 3, 7 - 12
Inventive step (IS)	Yes:	Claims	4, 5, 13, 14
	No:	Claims	1 - 3, 6 - 12, 15 - 17
Industrial applicability (IA)	Yes:	Claims	10 - 17
	No:	Claims	

**2. Citations and explanations**

**see separate sheet**

**VII. Certain defects in the international application**

The following defects in the form or contents of the international application have been noted:

**see separate sheet**

**VIII. Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

**see separate sheet**

The following documents of the state of the art have been taken into account during examination:

D1: WO-A-96/00582  
D2: US-A-5,493,008  
D3: US-A-5,082,926  
D4: WO-A-93/19783

**SECTION V:**

1. For the assessment of the present claims 1 - 9 on the question whether they are industrially applicable, no unified criteria exist in the PCT. Nevertheless the question whether the claims fulfil the criteria of novelty and inventive step with respect to the state of the art has been assessed.
2. Due to deletion of claim 10 as originally filed, the novelty objection based upon documents D1 and D2 is overcome.
3. The closest prior art for the pertinent claims results from Document D3.

It concerns a particular peptide fragment of collagen type IV and antibodies specific thereto, which inhibit basal lamina formation.

D3 discloses the capability of the competing peptide to promote nerve regeneration and indicates the clinical use in promoting regeneration of damaged nerves, this use will necessarily be based upon inhibition of basal lamina formation (Examples 1 - 6, col. 9, lines 18 - 20, col. 11, lines 42 - 45, col. 13, lines 4 - 35, col. 14, lines 13 - 20).

The content of D3 is therefore detrimental to the novelty of the method according to claims 1 - 3, contrary to Art. 33(2) PCT.

The discovery of a novel pathophysiological mechanism does not confer novelty to a previously known medical application.

- 4.1. Contrary to the applicant's arguments, the scope of the claims conferred by the functional definition of suitable agents as being "capable of specifically inhibiting basal lamina formation" is considered as vague and open to interpretation, thus contravening the requirements of Art. 6 PCT, the more as the description fails to give a definition of what is to be regarded as a "specific inhibition".

In the present case the lack of clarity results in an uncertainty as to whether the claims are limited with respect to the prior art of D4.

- 4.2. The applicant argued that TGF- $\beta$  the compound used in D4 for promoting neuronal regeneration had numerous "non-specific cell responses" and thus does not represent a "specific" inhibitor in the sense of the present application. Furthermore a specific inhibitor according to the present application should not exhibit deleterious side effects (due to a non-specific response).
- 4.3. However, many of the substances listed in claims 4 and 5 such as, e.g. Fe-chelating agents and Zn-salts have a wide spectrum of physiological activities (as has TGF- $\beta$ ), are expected to have deleterious side effects especially when administered systemically (e.g. due to e.g. the capability of Zn ions to unfold proteins or as there are a variety of Fe dependent proteins other than prolyl hydroxylase, cf. claim 8, see Section VIII, item 9). It remained also uncommented by which activity  $\beta$ -lactam antibiotics exert a specific inhibition of basement membrane formation, or which are the proteins the expression of which is to be inhibited by antisense oligonucleotides, in order to provide a specific inhibition of basement membrane formation.
- 4.4. Finally, the functional term "(the basal membrane building elements are...) accessory substances for proper function...or the assembly..., or both..." in claim 3 is vague and obscure and thus raises additional uncertainty as to the scope of claim 1 with respect to the term "specific inhibition of basal membrane formation".
- 4.5. Thus, it cannot be excluded that extracellular matrix proteins, the expression of which is modulated by TGF- $\beta$  antagonists, known as neuronal regeneration promoting agents from D4 (cf. p. 1, 3rd paragraph of the description and p. 3, lines 3 - 10) fall within the definition of such "accessory substances".

Thus the claims 1 - 3, 7 and 8 are, due to the vague and obscure functional definition of suitable agents, not clearly limited with respect to and not novel over the state of the art according to D4, contrary to Art. 6 and 33(2) EPC.

The above objections analogously apply to claims 10 - 12.

5. The determination of appropriate dosage and suitable modes of administration, is a matter of routine trials and therefore obvious to a skilled person (cf. also D4, p. 10, lines 14 - 20 and 25 - 28). Also the combination of the present agents with others known to be suitable for treatment of neuronal pathologies e.g. those acting as promoting neuronal regeneration appears to be prima vista obvious and is suggested in D4 (see D4, p. 10, lines 20 - 25); unexpected synergistic effects resulting from selected combinations have not been demonstrated.

Consequently, the subject-matter of claims 6, 9 as well as that of claims 15 - 17 (due to the vague and obscure functional definition of the first constituent) does not meet the requirements of Art. 33(3) PCT in view of D4.

6. None of the compounds listed in claim 4, 5, 13 and 14 have been disclosed or suggested for use in promoting neuronal regeneration (but please see Section VIII, item 9).

Consequently, claims 4, 5, 13 and 14 seem to be novel and inventive as required by Art. 33(2) and (3) PCT.

#### **SECTION VII:**

7. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1 - D3 is not mentioned in the description, nor are these documents identified therein.

#### **SECTION VIII:**

8. The independent claims are not acceptable under Art. 6 PCT, as the active agent is defined in terms of its physiological activity only (see Section V, item 4.1 - 4.4.).

Thereby the scope is rendered obscure to such an extent that there is no clear limitation with respect to the prior art of D4.

9. Claims 4, 5, 13 and 14 encompass a variety of substances which as such do not represent compounds capable of "specifically inhibiting basal lamina formation" and thus appear to extend beyond the scope of the independent claims to which they refer, thus causing uncertainty as to the actual scope of protection.

Thus, it would appear that Fe chelators as generally mentioned in claim 4 do not represent specific inhibitors of basal lamina formation. Even  $\text{Fe}^{2+}$  chelating agents which are capable of inhibiting the activity of  $\text{Fe}^{2+}$  dependent amino acid hydroxylases are expected to interfere with the activity of other iron dependent proteins, especially when administered systemically.

Furthermore, (systemic) inhibition of prolin and lysin hydroxylation would interfere with synthesis of any type of collagen, and thus of formation of connective tissue in general. Administration of corresponding enzyme inhibitors, especially if administered systemically would thus not warrant a "specific inhibition" of basal lamina formation.

It is additionally not clear upon which activity Zn salts or  $\beta$ -lactam antibiotics are capable of "specifically" inhibiting formation of basement membranes; the same applies to anthracyclins and anthraquinones.

The use of antisense oligonucleotides has not been exemplified. The application even fails to indicate which are the potential target site of antisense oligonucleotide mediated inhibition of protein expression to inhibit basal lamina without interfering with "normal" collagen and connective tissue formation. Thus, the use of antisense oligonucleotides (claim 5) is considered to lack substantial support, contrary to Art. 6 PCT.

**PCT**WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau

## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6: <b>C07K 16/18, A61K 48/00</b>	<b>A1</b>	(11) International Publication Number: <b>WO 98/51708</b> (43) International Publication Date: 19 November 1998 (19.11.98)
<p>(21) International Application Number: <b>PCT/EP98/02808</b></p> <p>(22) International Filing Date: <b>13 May 1998 (13.05.98)</b></p> <p>(30) Priority Data: <b>97107846.4</b> <b>14 May 1997 (14.05.97)</b> <b>EP</b> (34) Countries for which the regional or international application was filed: <b>DE et al.</b></p> <p>(71)(72) Applicants and Inventors: <b>MÜLLER, H., W. (DE/DE); Labor für Molekulare Neurobiologie, Neurologische Klinik, Heinrich-Heine-Universität Düsseldorf, Moorenstrasse 5, D-40225 Düsseldorf (DE). STICHEL-GUNKEL, Christine, C. (DE/DE); Molekulare Neurobiologie, Neurologische Klinik Universität Düsseldorf, Moorenstrasse 5, D-40225 Düsseldorf (DE).</b></p> <p>(74) Agents: <b>MEYERS, Hans-Wilhelm et al.; P.O. Box 10 22 41, D-50462 Köln (DE).</b></p>		<p>(81) Designated States: <b>AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, GW, HU, ID, IL, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</b></p> <p><b>Published</b> <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>
<p>(54) Title: <b>A METHOD FOR THE IMPROVEMENT OF NEURONAL REGENERATION</b></p> <p>(57) Abstract  A method for the improvement of neuronal regeneration by prevention or inhibition of basal membrane formation induced by a lesion of neuronal tissue.</p>		

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